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Ionic Liquid as Soluble Support for Synthesis of 1,2,3-Thiadiazoles and 1,2,3-Selenadiazoles

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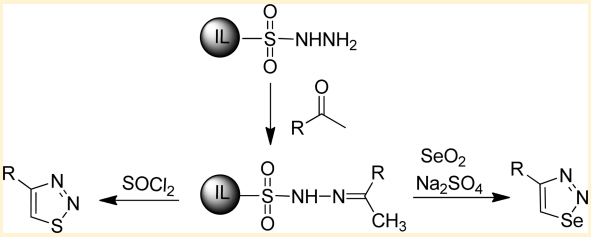
Supporting Information

ABSTRACT: A convenient synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles was achieved using an ionic liquid as a novel soluble support. Ionic liquid-supported sulfonyl hydrazine was synthesized and reacted with a number of ketones to afford the corresponding ionic liquid-supported hydrazones that were converted to 1,2,3-thiadiazoles in the presence of thionyl chloride. The reaction of ionic liquid-supported hydrazones with selenium dioxide in acetonitrile afforded 1,2,3-selenadiazoles. The advantages of this methodology were the ease of workup, simple reaction conditions, and high purity.



1,2,3-Thiadiazoles are important heterocycles[1] that possess broad pharmacological properties such as anticancer, antibacterial, fungicidal,[2] antihepatitis B virus,[3] and anti-HIV[4] activities. Figure 1 depicts chemical structures of selected bioactive 1,2,3-thiadiazoles. 1,2,3-Thiadiazoles are also useful intermediates in the synthesis of several organic compounds, such as 2-thioindole and 2-alkoxybenzo[*b*]thiophenes,[5] *β*-hydroxysulfides,[6] and thioamides.[7] 1,2,3-Selenadiazoles are bioisosteric heterocycles of 1,2,3-thiadiazoles and have attracted attention because of their diverse biological activities such as antibacterial,[8,9] antifungal,[10] anticancer,[11,12] and anti-HIV[13] activities. Furthermore, they have been utilized as intermediates for the synthesis of organic compounds such as dihydroselenophenes[14,15] and 2,3-dihydro-*1H*-pyrroles.[16] Selenadiazoles are a well-known source for strained alkynes and cycloalkynes.[17,18]

Several synthetic routes have been developed for the synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles.[19] Hurd and Mori reported a practical synthesis of 1,2,3-thiadiazoles by the cyclization of the corresponding tosylhydrazones from *α*-methylene ketones with thionyl chloride.[20] In analogy to synthesis of 1,2,3-thiadiazoles, the Yalpani group described the synthesis of 1,2,3-selenadiazoles by the oxidative cyclization of the tosylhydrazones with selenium dioxide.[21,22] Although the reported methods serve the synthetic requirements, they suffer from some disadvantages. For example, chromatographic separation is necessary to remove the sulfonyl chloride, which is tedious in multigram scale. To overcome these problems, several methodologies including "catch and release" have been developed for the expedited workup and purification of compounds synthesized in solution.[23,24] However, these methods are also associated with limitations. The need of excess reagents, longer times to drive reactions to completion, and inability to use in pilot scale have made their applicability narrow.

Ionic liquid-supported synthesis[25] is a new strategy offering several advantages for organic synthesis retaining the supremacy of product isolation and purification of solid-phase synthesis along with solubility benefits of traditional solution-phase chemistry. In this approach, a desired molecule is attached to an ionic liquid by an appropriate linker and the multistep synthesis of the target molecule is carried out without detaching the ionic liquid for monitoring the reaction progress at every stage. Unreacted reagents and unwanted compounds are easily separated out from the ionic liquid by simple washing with appropriate solvents before the final cleavage. The main feature of ionic liquid-supported synthesis resembles the polymer-supported synthesis, but high-loading efficiency, tunable solubility,[26] possibility to monitor the reaction progress by different analytical techniques, and minimal use of solvents have made this method an attractive and favorable alternative to solid-phase synthesis.

Ionic liquids with a different type of linker and desired functional group or moiety (**1**−**5**, Figure 2) have been synthesized and used for several organic transformations.[27−31] Bazureau et al.[27] were the first to propose the use of ionic liquid as a soluble support for the synthesis of small organic molecules. Tao et al.[28] described the advantages of ionic liquid-supported synthesis over polymer-supported synthesis in combinatorial chemistry by synthesizing *cis*-*β*-lactam library. Recently, we reported ionic liquid-supported synthesis of sulfonamides and carboxamides[29] using a novel ionic liquid-supported linker. There are only a few reports on ionic liquid-

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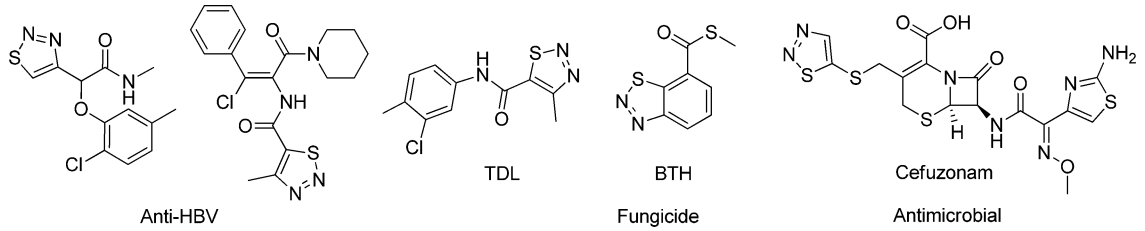


Figure 1. Chemical structures of some bioactive 1,2,3-thiadiazoles and biological activities.

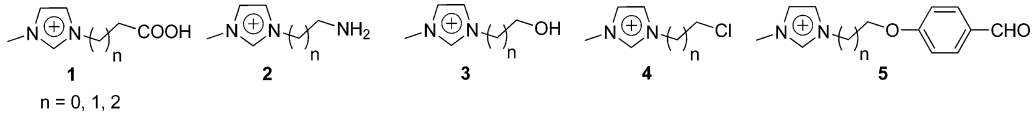
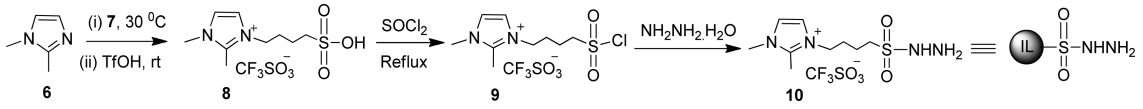


Figure 2. Some commonly used linkers in ionic liquid-supported synthesis.

Scheme 1. Synthesis of Ionic Liquid-Supported Sulfonyl Hydrazine



supported synthesis of heterocycles,[30,31] possibly because in most of the ionic liquid-supported syntheses the substrate should have a functionality to anchor on ionic liquid support that leads to an extra or unwanted functional group upon cleavage.

In continuation of our efforts on application of ionic liquids in organic synthesis,[32−34] we report a new, simple, and convenient approach for synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles using soluble ionic liquid-supported sulfonyl hydrazine. To the best of our knowledge, this is first report on use of ionic liquid-supported sulfonyl hydrazine as a catch and release linker.

Ionic liquid-supported sulfonyl hydrazine was synthesized by simple reaction sequences shown in Scheme 1. Initially, the reaction of 1-methylimidazole (**6**) with 1,4-butane sultone (**7**) at 30 °C followed by reaction with trifluoromethanesulfonic acid (TfOH) at room temperature for 2 h gave **8**.[35,36] Reaction of **8** with thionyl chloride under reflux conditions gave ionic liquid-supported sulfonyl chloride (**9**), which on reaction with hydrazine hydrate afforded **10**. The structure of **10** was confirmed by IR, ^{1}H NMR, and mass spectrometry. A singlet peak at 3.47 ppm corresponding to the *N*-methyl group, triplet at 3.88 ppm for aliphatic protons adjacent to the imidazole ring, and two doublets at 7.58 and 7.56 ppm for imidazole protons were observed in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, three peaks at 144, 122, and 121 ppm for imidazole ring carbons along with other aliphatic carbons were observed. A peak at *m*/*z* 247.1208 $[M-CF_3SO_3]^+$ was observed in ESI-TOF MS spectra, which confirmed the structure of **10**.

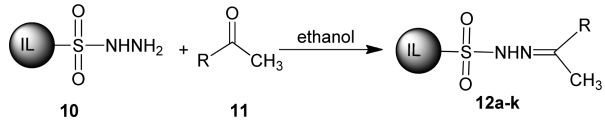
The synthetic procedure for 1,2,3-thiadiazole derivatives started from ionic liquid-supported sulfonyl hydrazone derivatives (**12**) that were obtained by reacting ionic liquid-supported sulfonyl hydrazine (**10**) with the corresponding carbonyl compounds (**11**). Different ketones were converted into the corresponding ionic liquid-supported hydrazones **12a**−**k** in high to excellent yields (Table 1) at room temperature (Scheme 2). The structures of ionic liquid-supported sulfonyl hydrazones were confirmed by ^{1}H NMR, ^{13}C NMR, and mass analysis. A characteristic peak in the range of 10.2−10.7 ppm was observed in the ^{1}H NMR spectra for the NH proton along

Table 1. Synthesis of Ionic Liquid-Supported Hydrazones 12a−k

compd	R	yield[a] (%)	compd	R	yield[a] (%)
12a	C_6H_5	86	**12g**	4-ClC_6H_4	88
12b	4-$OCH_3C_6H_4$	81	**12h**	4-BrC_6H_4	88
12c	4-$CH_3C_6H_4$	82	**12i**	4-$NO_2C_6H_4$	86
12d	1-$C_{10}H_7$	88	**12j**	C_5H_4N	92
12e	2-$C_{10}H_7$	86	**12k**	C_4H_3S	94
12f	4-FC_6H_4	90			

[a]Isolated yield.

Scheme 2. Synthesis of Ionic Liquid-Supported Sulfonyl Hydrazones 12a−k



with other protons, and a peak in the range of 150.2−156.5 ppm appeared for the C═NH carbon along with other carbons. In ESI-TOF MS, a peak appeared corresponding to the $[M-CF_3SO_3]^+$ ion.

To optimize reaction conditions to synthesize 1,2,3-thiadiazoles, **12a** (1.0 equiv) was first reacted with $SOCl_2$ (5.0 equiv) in dichloroethane (DCE) at room temperature. The reaction was very sluggish and took 10 h to be completed. However, when the reaction was heated at 60 °C, it took only 4 h for completion of the reaction. Next, we attempted the reaction without solvent, and it was found that there was not much difference in the yield of **13a** as well as in the time of reaction in the absence of solvent. In fact, ionic liquid-supported hydrazones **12a** were readily reacted under solvent-free conditions with thionyl chloride producing **13** in excellent yield at 60 °C (Scheme 3, Table 2). The reaction mixture was neutralized by sodium bicarbonate solution, and the compound was removed from ionic liquid layer by extracting in ethyl acetate/hexane layer. The compounds were pure and the chromatographic purification was not required. The formation

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Scheme 3. Synthesis of 1,2,3-Thiadiazoles

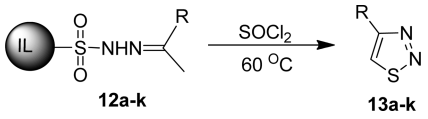
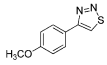


Table 2. Synthesis of 1,2,3-Thiadiazoles 13a−k

Compd	R	Product	Yield (%)[b]	Compd	R	Product	Yield (%)[b]
13a	C_6H_5		91	**13g**	4-ClC_6H_4		88
13b	4-$OCH_3C_6H_4$		86	**13h**	4-BrC_6H_4		90
13c	4-$CH_3C_6H_4$		87	**13i**	4-$NO_2C_6H_4$		83
13d	$C_{10}H_7$		84	**13j**	C_5H_4N		80
13e	$C_{10}H_7$		88	**13k**	C_4H_3S		88
13f	4-FC_6H_4		89				

[a]Reaction conditions: ionic liquid-supported sulfonyl hydrazone (**12**) (1 mmol), thionyl chloride (5 mmol), 60 °C, 4 h. [b]Isolated yield.

of the thiadiazole **13a** was confirmed by spectroscopy techniques. A characteristic singlet peak in the range of 8.5−8.8 ppm was observed in ^{1}H NMR for the C_5-proton of the 1,2,3-thiadiazole ring, and the corresponding carbon was observed in the range of 130.3−136.4 ppm in the ^{13}C NMR. To investigate the generality of the method, we synthesized a library of 1,2,3-thiadiazoles from the corresponding ionic liquid-supported sulfonyl hydrazones **12a−k** and thionyl chloride (Table 2). Both electron withdrawing and electron releasing aromatic ketones were found to be excellent substrates for the synthesis of 1,2,3-thiadiazoles.

Considering our success with 1,2,3-thiadiazoles, we employed a similar strategy for the synthesis of 1,2,3-selenadiazoles. The reaction of ionic liquid-supported sulfonyl hydrazones **12** with selenium dioxide for the synthesis of 1,2,3-selenadiazoles **14a−f** was challenging. Initially, reaction of **12a** with selenium dioxide in the presence of acetic acid with the expectation of 4-phenyl-1,2,3-selenadiazole (**14a**) did not result in the formation of desired heterocycle; instead, it was hydrolyzed to generate the starting acetophenone **11a**. Thus, the reaction was carried out under different reaction conditions and in different solvents. Using selenium dioxide in acetonitrile without acetic acid led to the conversion of **12a** into **14a** in modest yield and purity. We then applied this methodology to different ionic liquid-supported hydrazones **12** to generate the corresponding selenadiazoles **14b−f** (Scheme 4) in moderate yield (Table 3). There was a slight increase in the yield after using dry sodium sulfate as it absorbs the water released in the

Scheme 4. Synthesis of Selenadiazoles 14a−f

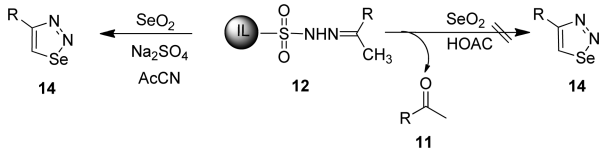


Table 3. Synthesis of Selenadiazoles 14a−f[a]

Compd	R	Product	Yield (%)[a]	Compd	R	Product	Yield (%)[b]
14a	C_6H_5		30	**14d**	C_4H_3S		32
14b	4-$CH_3OC_6H_4$		22	**14e**	$C_{10}H_7$		25
14c	4-ClC_6H_4		30	**14f**	4-BrC_6H_4		40

[a]Reaction conditions: ionic liquid-supported hydrazone (1 mmol), selenium dioxide (1.05 mmol), sodium sulfate (1.5 mmol), acetonitrile (6 mL), 24 h. [b]Isolated yield.

reaction. The yield were comparable with the reported solution phase yield of 1,2,3-selenadiazoles and purity was over 90% as shown by HPLC analysis.

The chemical structures of 1,2,3-selenadiazoles were confirmed using ^{1}H and ^{13}C NMR and mass spectroscopy. In ^{1}H NMR, the proton attached to C_5 gives a strong singlet around 9.00−9.50 ppm along with other protons, while the C_5 carbon appeared in the range of 135.0−146.0 ppm along with other carbons in ^{13}C NMR.

In summary, we have demonstrated a simple and convenient approach for ionic liquid-supported synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles. The advantage of this methodology is the ease of workup, simple reaction conditions, and high purity. Indeed, 1,2,3-thiadiazoles were obtained pure by neutralization with sodium hydrogen carbonate, isolation with organic solvents, and subsequent evaporation of the organic solvent. Thus, this methodology provides access toward the synthesis of diverse 1,2,3-thiadiazole and 1,2,3-selenadiazole derivatives under simple reaction conditions. This study provides insights for using ionic liquid-supported reagents for the synthesis of other heterocyclic compounds.

EXPERIMENTAL SECTION

Synthesis of Ionic Liquid-Supported Sulfonic Acid (8). Ionic liquid-supported sulfonic acid was prepared according to previous procedures with slight modifications.[35,36] 1,4-Butanesultone (1 equiv) was added dropwise to 1,2-dimethylimidazole (1 equiv) at 30 °C. The resulting solution was stirred until a solid was obtained at room temperature. After completion of reaction, the product was washed with toluene (3 × 15 mL) and finally with diethyl ether (3 × 15 mL) to remove unreacted starting materials. The compound was dried under reduced pressure to obtain the zwitterionic form. Trifluoromethanesulfonic acid (1.1 mmol) was added dropwise to the zwitterion at 0 °C. After completion of the addition, the solution was stirred at 40 °C until a thick liquid was obtained. The resulting liquid was washed with diethyl ether to remove excess triflic acid. The compound was dried under reduced pressure to give a pale yellow thick liquid **8** (7 g, 98%).

Synthesis of Ionic Liquid-Supported Sulfonyl Chloride (9). Thionyl chloride ($SOCl_2$, 3 equiv) was added dropwise by an additional funnel to the ionic-liquid sulfonic acid (**8**, 1 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 8 h and finally heated to 80 °C for 2 h. Excess thionyl chloride was removed by a rotatory evaporator under reduced pressure with nitrogen atmosphere to obtain a yellow, thick, ionic liquid-supported sulfonyl chloride **9** (7.08 g, 96%).

Synthesis of Ionic Liquid-Supported Sulfonyl Hydrazide (10). Hydrazine hydrate (2 equiv) was added slowly to **9** at 0 °C in THF. After completion of addition, the reaction mixture was slowly heated up to 40 °C for 4 h. After completion of the reaction, THF was

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evaporated under reduced pressure. The resulting mixture was washed with ethyl acetate (3 × 15 mL) to remove hydrazine in order to get pure white solid **10** (6.73 g, 96%): mp 94−97 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.19 (bs, 2H), 4.15 (t, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.13 (t, J = 7.7 Hz, 2H), 2.59 (S, 3H), 1.85−1.80 (m, 2H), 1.65−1.61 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 144.8, 122.8, 121.3, 47.4, 46.7, 35.2, 28.1, 20.2, 9.7; HRMS (ESI-TOF) (m/z): calcd for $C_9H_{19}N_4O_2S^+$ 247.1229, found 247.1208 [M−CF_3SO_3]$^+$.

Synthesis of Ionic Liquid-Supported Hydrazones 12a−k. Acetophenone (1.05 equiv) and liquid-supported sulfonyl hydrazide (1 equiv) were taken in ethanol (10 mL) and vigorously stirred at room temperature until the solid precipitated out. The reaction mixture was filtered and washed with cold ethanol (2 × 5 mL) and dried under reduced pressure to get the pure product.

Compound 12a: white solid (34 mg, 86%); mp 145−150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.73−7.71 (m, 2H), 7.63 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 4.15 (t, J = 7.0 Hz, 2H), 3.71 (s, 3H), 3.36−3.27 (m, 2H), 2.56 (s, 3H), 2.23 (s, 3H), 1.86−1.82 (m, 2H), 1.75−1.69 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.7, 144.8, 138.0, 129.8, 128.8, 126.6, 122.7, 121.3, 49.7, 47.3, 35.1, 28.1, 20.1, 15.0, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{25}N_4O_2S^+$ 349.1698, found 349.1719 [M − CF_3SO_3]$^+$.

Compound 12b: light yellow solid (310 mg, 81%); mp 126−130 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.75 (d, J = 9 Hz, 2H), 7.69 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.02 (d, J = 9 Hz, 2H), 4.22 (t, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.41−3.33 (m, 2H), 2.63 (s, 3H), 2.26 (s, 3H), 1.97−1.89 (m, 2H), 1.82−1.77 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.7, 153.7, 144.8, 130.4, 128.1, 122.7, 121.3, 114.1, 55.7, 49.3, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{18}H_{27}N_4O_3S^+$ 379.1804, found 379.1779 [M − CF_3SO_3]$^+$.

Compound 12c: light yellow solid (320 mg, 82%); mp 139−142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.63−7.59 (m, 4H), 7.21 (d, J = 7.7 Hz, 2H), 4.15 (t, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.45−3.09 (m, 2H), 2.56 (s, 3H), 2.32 (s, 3H), 2.20 (s, 3H), 1.91−1.79 (m, 2H), 1.79−1.61 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.7, 144.8, 139.5, 135.2, 129.4, 126.5, 122.7, 121.3, 49.4, 47.3, 35.1, 28.1, 21.3, 20.1, 14.9, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{18}H_{27}N_4O_2S^+$ 363.1855, found 363.1874 [M − CF_3SO_3]$^+$.

Compound 12d: white solid (360 mg, 88%); mp 126−132 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.11−8.05 (m, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.57−7.48 (m, 4H), 4.14 (t, J = 6.9 Hz, 2H), 3.71 (s, 3H), 3.30−3.23 (m, 2H), 2.54 (s, 3H), 2.39 (d, J = 17.9 Hz, 3H), 1.89−1.80 (m, 2H), 1.79−1.70 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.1, 144.8, 137.4, 133.8, 130.4, 129.4, 128.9, 127.1, 126.5, 126.3, 125.7, 125.6, 122.8, 121.3, 49.5, 47.3, 35.1, 28.2, 20.1, 19.8, 9.6; HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{27}N_4O_2S^+$ 399.1855, found 399.1830 [M − CF_3SO_3]$^+$.

Compound 12e: light yellow solid (360 mg, 86%); mp 146−150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 7.1 Hz, 2H), 7.66−7.48 (m, 4H), 4.17 (t, J = 7.2 Hz, 2H), 3.70 (s, 3H), 3.38 (t, J = 7.2 Hz, 2H), 2.56 (s, 3H), 2.35 (s, 3H), 1.94−1.81 (m, 2H), 1.80−1.66 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2, 144.8, 135.3, 133.7, 133.1, 129.0, 128.2, 128.0, 127.4, 127.0, 126.6, 123.8, 122.8, 121.3, 49.6, 47.3, 35.1, 28.1, 20.1, 14.7, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{21}H_{27}N_4O_2S^+$ 399.1855, found 399.1844 [M − CF_3SO_3]$^+$.

Compound 12f: white solid (350 mg, 91%); mp 138−142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.78 (dd, J = 8.5, 4.8 Hz, 2H), 7.62 (d, J = 3.0 Hz, 1H), 7.60 (d, J = 3.0 Hz, 1H), 7.24 (td, J = 9.0, 2.5 Hz, 2H), 4.15 (t, J = 7.5 Hz, 2H), 3.72 (s, 3H), 3.35−3.26 (m, 2H), 2.57 (s, 3H), 2.22 (s, 3H), 1.88−1.82 (m, 2H), 1.75−1.69 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.6, 144.8, 134.5, 134.4, 128.8, 122.7, 121.3, 115.8, 49.5, 47.3, 35.1, 28.1, 20.1, 15.0, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{24}FN_4O_2S^+$ 367.1604, found 367.1635 [M − CF_3SO_3]$^+$.

Compound 12g: white solid (340 mg, 88%); mp 155−157 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.65 (brs, 1H), 7.62 (brs, 1H), 7.46 (d, J = 9.0 Hz, 2H), 4.16 (t, J = 7.0 Hz, 2H), 3.74 (s, 3H), 3.36−3.29 (m, 2H), 2.58 (s, 3H), 2.23 (s, 3H), 1.92−1.84 (m, 2H), 1.80−1.70 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.5, 144.8, 136.8, 134.5, 128.8, 128.4, 122.7, 121.3, 49.5, 47.3, 35.1, 28.1, 20.0, 14.9, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{24}ClN_4O_2S^+$ 383.1308, found 383.1332 [M − CF_3SO_3]$^+$.

Compound 12h: white solid (380 mg, 88%); mp 159−163 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.74−7.51 (m, 6H), 4.15 (t, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.37−3.22 (m, 2H), 2.57 (s, 3H), 2.22 (s, 3H), 1.90−1.78 (m, 2H), 1.78−1.65 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.4, 144.8, 137.2, 131.8, 128.6, 123.3, 122.6, 121.3, 49.5, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{24}BrN_4O_2S^+$ 427.0803, found 427.0800 [M − CF_3SO_3]$^+$.

Compound 12i: light pink solid (350 mg, 86%); mp 167−171 °C; ^{1}H NMR (500 MHz, DMSO) δ 10.73 (s, 1H), 8.26 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.7 Hz, 1H), 4.19 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 3.44−3.32 (m, 2H), 2.60 (s, 2H), 2.31 (s, 3H), 1.94−1.83 (m, 2H), 1.82−1.75 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 150.8, 148.0, 144.8, 144.0, 127.7, 124.0, 122.7, 121.3, 49.8, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{24}N_5O_4S^+$ 394.1549, found 394.1528 [M − CF_3SO_3]$^+$.

Compound 12j: black solid (350 mg, 92%); mp 105−111 °C; ^{1}H NMR (500 MHz DMSO-d_6) δ 10.66 (s, 1H), 8.63 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.90 (td, J = 9, 2.5 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 7.0, 5.0 Hz, 1H), 4.17 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.51−3.30 (m, 2H), 2.58 (s, 3H), 2.33 (s, 3H), 1.96−1.83 (m, 2H), 1.78−1.73 (m, 2H).; ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5, 153.0, 148.7, 144.8, 137.8, 124.8, 122.7, 121.3, 120.9, 49.8, 47.3, 35.1, 28.1, 20.1, 13.3, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{16}H_{24}N_5O_2S^+$ 350.1651, found 350.1637 [M − CF_3SO_3]$^+$.

Compound 12k: yellow color solid (360 mg, 94%); mp 121−134 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 5.0, 1.0 Hz, 1H), 7.46−7.42 (m, 1H), 7.08−7.04 (m, 1H), 4.14 (t, J = 7.5 Hz, 2H), 3.71 (s, 3H), 3.26 (td, J = 7.5, 2.1 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H), 1.91−1.79 (m, 2H), 1.79−1.66 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.3, 144.8, 142.8, 129.1, 128.3, 128.1, 122.8, 121.3, 49.6, 47.3, 35.1, 28.2, 20.1, 15.2, 9.6; HRMS (ESI-TOF) (m/z) calcd for $C_{15}H_{23}N_4O_2S_2^+$ 355.1262, found 355.1251 [M − CF_3SO_3]$^+$.

Synthesis of 1,2,3-Thiadiazoles 13a−k. To ionic liquid-supported hydrazone (1 mmol) was added thionyl chloride (5 mmol) dropwise at room temperature, and the reaction mixture was heated slowly to 60 °C for 4 h. Progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was neutralized by sodium bicarbonate solution. The compound was extracted using ethyl acetate/hexane (3:2 v/v, 3 × 5 mL), dried over sodium sulfate, and evaporated under reduced pressure to obtain pure compound.

Compound 13a: white solid (58 mg, 91%); mp 77−78 °C (lit.[37] mp 75−77 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.7 Hz, 2H), 7.45 (t, J = 7.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 147.5, 136.6, 136.3, 128.1, 124.4; HRMS (ESI-TOF) (m/z) calcd for $C_8H_7N_2S^+$ 163.0330, found 163.0321 [M + H]$^+$.

Compound 13b: white solid (62 mg, 86%); mp 87−91 °C (lit.[37] mp 91−93.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 160.5, 128.8, 128.4, 123.6, 114.6, 55.5; HRMS (ESI-TOF) (m/z) calcd for $C_9H_9N_2OS^+$ 193.0436, found 193.0423 [M + H]$^+$.

Compound 13c: white solid (55 mg, 87%); mp 73−76 °C (lit.[37] mp 74−76 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.94 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 139.5, 129.8, 129.2, 128.0, 127.3, 21.3; HRMS (ESI-TOF) (m/z) calcd for $C_9H_9N_2S^+$ 177.0486, found 177.0458 [M + H]$^+$.

Compound 13d: white solid (64 mg, 84%); mp 197−201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H),

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7.99 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.77 (dd, J = 7.1, 1.0 Hz, 1H), 7.63−7.49 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 133.2, 133.1, 132.8, 130.4, 129.0, 127.5, 127.4, 126.0, 125.2, 124.2, 124.1; HRMS (ESI-TOF) (m/z) calcd for $C_{12}H_9N_2S^+$ 213.0486, found 213.0474 $[M + H]^+$.

Compound 13e: white solid (67 mg, 88%); mp 203−207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.61 (s, 1H), 8.11 (dd, J = 8.4, 1.3 Hz, 1H), 8.01−7.93 (m, 2H), 7.91−7.88 (m, 1H), 7.67−7.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 133.7, 133.5, 130.1, 130.0, 129.0, 128.5, 128.1, 127.8, 126.9, 126.9, 124.7; HRMS (ESI-TOF) (m/z) calcd for $C_{12}H_9N_2S^+$ 213.0486, found 213.0455 $[M + H]^+$.

Compound 13f: white solid (67 mg, 89%); mp 185−189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.11−7.97 (m, 2H), 7.26−7.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 162.4, 129.7, 129.3, 127.0, 116.4; HRMS (ESI-TOF) (m/z) calcd for $C_8H_6FN_2S^+$ 181.0236, found 181.0220 $[M + H]^+$.

Compound 13g: white solid (64 mg, 88%); mp 138−140 °C (lit.[37] mp 136−137.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 135.4, 130.2, 129.4, 129.37, 128.6; HRMS (ESI-TOF) (m/z) calcd for $C_8H_6ClN_2S^+$ 196.9935, found 196.9905 $[M + H]^+$.

Compound 13h: white solid (74 mg, 90%); mp 150−154 °C (lit.[23] mp 150−152 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 133.9, 131.4, 130.0, 128.6, 125.1; HRMS (ESI-TOF) (m/z) calcd for $C_8H_6BrN_2S^+$ 240.9435, found 240.9434 $[M + H]^+$ and 242.9587 $[M + H + 2]^+$.

Compound 13i: white solid (74 mg, 83%); mp 207−211 °C (lit.[37] mp 183 °C); ^{1}H NMR (500 MHz, DMSO) δ 9.92 (s, 1H), 8.53−8.25 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 159.6, 147.5, 136.6, 136.3, 128.1, 124.4; HRMS (ESI-TOF) (m/z) calcd for $C_8H_6N_3O_2S^+$ 208.0181, found 208.0166 $[M + H]^+$.

Compound 13j: white solid (51 mg, 80%); mp 158−161 °C (lit.[38] mp 163 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.69 (d, J = 4.7 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.92−7.85 (m, 1H), 7.35 (t, J = 6.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 149.9, 149.8, 137.4, 133.9, 123.9, 122.4; HRMS (ESI-TOF) (m/z) calcd for $C_7H_6N_3S^+$ 164.0282, found 164.0269 $[M + H]^+$.

Compound 13k: white solid (58 mg, 88%); mp 72−74 °C (lit.[39] mp 70−71 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.64 (dd, J = 3.6, 1.2 Hz, 1H), 7.43 (m, 2H), 7.14 (dd, J = 4.8, 1.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.2, 139.0, 135.8, 128.6, 127.5, 126.8, HRMS (ESI-TOF) (m/z) calcd for $C_6H_5N_2S_2^+$ 168.9889, found 168.9875 $[M + H]^+$.

Synthesis of Selenadiazoles 14. Ionic liquid-supported hydrazone (1 mmol), selenium dioxide (1.05 mmol), and sodium sulfate (1.50 mmol) were mixed in acetonitrile (6 mL) and vigorously stirred at room temperature for 24 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the residue was purifed using toluene as a mobile phase to obtain pure product.

Compound 14a: yellow solid (29 mg, 30%); mp 70−71 °C (lit.[21] mp 76 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 137.0, 132.1, 129.1, 127.7; HRMS (ESI-TOF) (m/z) calcd for $C_8H_7N_2Se^+$ 210.9774, found 210.9753 $[M + H]^+$.

Compound 14b: yellow solid (20 mg, 22%); mp 85−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 160.1, 135.1, 129.1, 124.9, 114.6, 55.3; HRMS (ESI-TOF) (m/z) calcd for $C_9H_9N_2OSe^+$ 240.9875, found 240.9843 $[M + H]^+$.

Compound 14c: black solid (26 mg, 30%); mp 118−125 °C (lit.[38] mp 154 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 136.2, 133.8, 129.5, 128.4, 127.9; HRMS (ESI-TOF) (m/z):Calcd for $C_8H_6ClN_2Se^+$ 244.9385, found 244.9386 $[M + H]^+$.

Compound 14d: viscous liquid (27 mg, 32%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.80−7.75 (m, 1H), 7.66 (dd, J = 5.1, 1.2 Hz, 1H), 7.20 (ddd, J = 5.2, 3.6, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 138.9, 136.5, 134.8, 128.6, 127.5, 126.8; HRMS (ESI-TOF) (m/z) calcd for $C_6H_5N_2SSe^+$ 216.9333, found 216.9302 $[M + H]^+$.

Compound 14e: solid (23 mg, 25%); mp 134−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.63 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.02−7.94 (m, 2H), 7.89 (d, J = 8.2 Hz, 1H), 7.58−7.48 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 137.1, 133.6, 133.4, 129.3, 128.94, 128.5, 127.8, 127.2, 126.8, 126.7, 125.1; HRMS (ESI-TOF) (m/z) calcd for $C_{12}H_9N_2Se^+$ 260.9931, found 260.9902 $[M + H]^+$.

Compound 14f: Solid (39 mg, 40%); mp 128−133 °C (lit.[38] mp 177 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 137.3, 132.4, 131.0, 129.2, 123.0; HRMS (ESI-TOF) (m/z) calcd for $C_8H_6BrN_2Se^+$ 288.8880, found 288.8876 $[M + H]^+$ and 290.8872 $[M + H + 2]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **10**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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